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POWER OF ATTORNEY OR AUTHORIZATION OF AGENT

Application Number	09/616283
Filing Date	July 14, 2000
First Named Inventor	T. Goodnow
Title	SYSTEM FOR DETECTING BACTERIA IN BLOOD, BLOOD PRODUCTS, AND FLUIDS OF TISSUES
Group Art Unit	1645
Examiner Name	J. Hines
Attorney Docket No.	VRXB-P01-001

#12 linda 10/24/02

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SIGNATURE of Applicant or Assignee of Record

Name	J. Straight
Signature	
Date	September 9, 2002

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required. See below*

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[X] Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

SIGNATURE of Applicant or Assignee of Record

Name	J. Straight
Signature	J. Straight
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VRXB-P01-001
State of the Art Publications

1.) http://www.ihita.org/023099.htm – 1/6/2000 publication on-line. Testimony on February 23, 1999.

Testimony provided by Jane Henney, FDA's commissioner to the U.S. House of Representatives hearing. On issues of blood safety: "The safety a d adequacy of the blood supply and blood products is one of the highest priorities of the FDA and the Department of Health and Human Resources." (Bottom of page 1) "The technology associated with disease detection in blood donors is continually improving, but risks remain. For a number of serious and life-threatening infections, there is a limited period after a possible donor has been infected, which the infection is not detectable by available methods. ... The risk to patients from bacterial contamination of blood and from blood band error must also be reduced."

2.) Goldman and Blajchman, 1991; Transfusion Medicine Review, Vol. V, No. 1: 73-83.

In the last 2 decades, there appears to have been a dramatic increase in the number of incidents of bacterial sepsis associated with the increase in the number of platelet transfusions given (Abstract)

"There are several difficulties involved in the bacteriologic screening of blood products. Traditional culture techniques require a lengthy incubation period of several days. False positives may occur because of contamination during the innoculation procedure itself. False negatives may occur because of the low numbers of bacteria present and suboptimal media or incubation temperatures for a given organism (see bottom of right column of page 80 to top of page 81).

3.) P. Ann Hoppe 1992; Transfusion 32(3): 199-201

Although numerous studies have been performed by the FDA and others, no rapid and reliable tests exist that could be readily applied in the blood bank setting (see bottom of right column of page 199).

The prospect of using a simple color comparison to detect bacterial contamination remains problematic, and the search for alternative procedures for detecting contaminating bacteria should continue. ... While there is promise in the observations of Kim et al., it is premature to conclude that this procedure will provide another increment in the safety of blood used for transfusions (see final paragraph on page 201).

4.) Bjajchman et al. 1994; Transfusion, 34(11): 940-942

"[T]ransfusion-associated bacterial sepsis has again begun to be recognized as a problem for blood component recipients. ... The recent steep increase in the number of

reports of sepsis due to the transfusion of infected blood components has involved both red cell and platelet transfusions" (see left column of page 940).

[R]outine random-donor PC units prepared ... showed that approximately 1 in 1,000 units was contaminated with bacteria. [T]ransfusion-associated bacteremia is *the most common* transfusion-related infection currently confronting the transfusion medicine community (see top of left column on page 941)

Effective methods for bacteriologic monitoring, using appropriately evidence-based studies, would have to be developed (see paragraph 2, right column of page 941).

5.) AABB Association Bulletin #96-6, dated August 7, 1996

To date, there has been no surveillance system or epidemiologic study to assess the risk of bacterial contamination of blood and blood components in the United States (see section 1).

Part of the difference in the number of estimated versus reported deaths is most likely due to the lack of a standardized approach to evaluating instances of suspected transfusion-associated sepsis (see section 2)

The overall frequency of septic complications resulting from bacterial contamination varies widely between institutions and may be due to variability in identification and reporting, or may reflect true variations incidence (see section 4).

At present, there is no fully satisfactory method for such monitoring (see section 2, second sentence). Subsections a-c describe the disadvantages associated with each testing technique – e.g., not sensitive enough, too expensive, no clear end-point for a negative finding, not yet validated.

Major emphasis should be given to developing and evaluating practical, sensitive and specific screening assays for the detection of bacteria in platelet concentrates and to developing methods to decontaminate cellular blood components (see section 7a).

6.) Klein et al. Transfusion 1997, 37: 95-101

On September 27, 1995, a conference on the microbial contamination of blood components was held at the Warren G. Magnuson Clinical Center of the National Institutes of Health. Dr. Cookson indicated that screening questions aimed at eliminating symptomatic donors would not be specific enough to prove effective. (see top of right column, page 96) Dr. Yomtovian, stated that a program of bacteriologic surveillance which the hospital put in place revealed a unit contamination rate of 1 in 2414, and a correlation with length of storage was observed (right column of page 96).

Methods that have a high rate of false-positive results would have limited practicality for blood component screening. To be cost effective for blood bank indications, the optimal test would have to be simple enough to be performed in a transfusion service or blood center. Sampling difficulties that can result in false-positive tests and the difficulty of assigning an exact quantity for all bacteria in order to define the acceptable level of sensitivity for detection systems. Although five cases of sepsis were

prevented, some cases were missed and a number of false-positive results were reports (see page 97).

The test procedure using an RNA probe was to cumbersome for routine blood bank screening and its use is no longer being pursued by the manufacturer. Visual inspection of PCs by the swirl test did not prove useful for detecting bacterial contamination. Glucose testing was not found to be a viable alternative (see page 98).

WBC reduction had no impact on bacterial growth. Further, it is not predictable as to which species of bacteria would be affected by WBC reduction. Filtration had no impact on the bacterial levels – in no case were the bacteria eliminated, and in fact, bacteria reached the same titer at the stationary phase of growth, whether or not the pool was filtered (see page 99).

A reduction in storage time would be acceptable only if the current processing time were materially decreased; such an outcome does not appear to be possible (see right column of page 100).

Dr. Sayers called for further investigation into novel screening and detection methods, especially because the conference suggested that chemiluminescence, once thought promising, is no longer being pursued for this purpose.

7.) Stephen Wagner, Zbl. Bakt. 1996, 283: 253-257

No practical test is available for bacteria detection in donor blood. Development of a bacterial test will be a formidable task, and will not likely parallel the antibody-based tests frequently used for detection of viral infections (see page 253).

Unfortunately, it is difficult to estimate what level of bacteria constitutes dangerously high levels because so few blood units have been quantitatively titered that have been associate with septic events. (see page 254, first paragraph).

None of the methods for detecting bacterial contamination are feasible for immediate implementation (see page 255).

Detection of bacterial antigens represent an interesting potential method. One difficulty of developing immunological-based tests is that there are likely to be no common antigens on the surface of the diverse species that have been implicated in transfusion-associated sepsis. No practical methods are available for detecting bacteria which can routinely implemented. One of the problems in reducing transfusion-associated bacterial sepsis is that a broad range of species with vastly different surface properties may be present (page 256).

8.) Barrett et al. Transfusion 1993; 33(3): 228-233

These studies suggest that bacterial contamination can result in adverse clinical sequelae in transfusion recipients and that both culturing and Gram staining are poor methods of screening for contaminated units. More sensitive and specific methods of generalized screening for bacterial contamination are needed (see abstract).

9.) Jacobs et al. Transfusion 2001; 41: 1331-1334

Transfusion of bacterially contaminated blood components, especially platelets, is an ongoing problem with variable clinical sequelae, including serious morbidity and mortality. The gaps in our knowledge of the actual incidence of blood component contamination and the clinical consequences thereof are due to variability in case definition, in the bacterial species involved, in the protocols for detecting and confirming bacterial contamination, and in the age of transfused platelet units, with 4- and 5-day-old units exhibiting the greatest risk (see page 1331).

There is no uncertainty regarding the need to identify one or more strategies to prevent or detect bacterial contamination of blood components. The ideal bacteria-detection method should be simple, rapid, sensitive, specific, inexpensive, and broadly applicable to all species of bacteria. Unfortunately, most of the detection methods discussed ... are too insensitive, as well as having many other limitations. Even microbiologic culture would not guarantee detection of all contaminated units, because of variability in the inoculum, in the kinetics of bacteria growth, and in the length of the lag phase (see page 1332).

In an era in which the risk of transmission of many blood-borne viruses, particularly HIV, has virtually been eliminated, it is paradoxical that the earliest recognized infectious transfusion complication, bacterial contamination, is now the most frequent and is providing the most difficult to eradicate (see page 1333).

10.) Wagner and Robinette, Transfusion 1998; 38: 674-679

Despite these measures [plastic containers], transfusion-associated bacterial sepsis continues to be a concern in transfusion medicine. Septic deaths, although infrequent, have been a recurrent theme in the literature during the last 30 years (see page 674)

Despite many attempts, no detection technique has been developed that meets all the requirements for a successful test. Detection of an organism by automated culture may require a 1- to 2-day incubation following bottle inoculation, which could reduce the availability of platelet components if units are quarantined until bacterial testing is completed (see bottom of page 674 to top of page 675).

The automated system of the invention disclosed in the paper was unable to predict the presence of organisms in contaminated PCs in some experiments (see page 677).

Another issue of concern is the frequency of false-positive units that might be unnecessarily destroyed. It is unclear whether automated blood culturing, if adopted, should take place in hospitals or blood centers. Platelet utilization, inventory control, and transfusion practice vary greatly among hospitals and might make standardization of testing difficult. The feasibility of using an automated blood culture for bacterial detection in PC(s) may ultimately depend more on whether there would be enough time after testing to routinely supply platelets for all patients than where testing might best be performed (see page 678).

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